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(54) 5HT-1A and 5HT-2 antagonists for treating side-effects of serotonin re-uptake inhibitors

(57) Side effects of serotonin re-uptake inhibitors (SRIs), e.g. fluoxetine which are used to treat depression may be prevented or reduced by administering a 5-HT_{1A} or 5-HT_2 antagonist, particularly, N-tert-butyl-3-[4-(2-methoxyphenyl)piperazin-1-yl]-2-phenylpropanamide, 2,3,4,5,6,7-hexahydro-1- [4[1-[4-(2-methoxyphenyl)-piperazinyl]]-2-phenyl]butanoyl-1H-azepine or N-[2[4-(2-methoxyphenyl)- 1-piperazinyl]ethyl]-N-(2-pyridinyl) cyclohexanecarboxamide. Onset of the therapeutic effects of the SRI's is also hastened by administration of the above antagonists, e.g. in the form of tablets and capsules.

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MEDICAL TREATMENT

The present invention relates to a method of treating neurological disorders.

Serotonin re-uptake inhibitors (SRI's) are commonly used to treat psychiatric disorders such as depression. Unfortunately, however, these compounds can give rise to side effects in use. Moreover, the onset of the therapeutic effect can be delayed undesirably.

It has now surprisingly been found that the side-effects associated with SRIs can be prevented and/or reduced by administration of a 5-HT_1 receptor antagonist

Accordingly, in a first aspect, the present invention provides a method of preventing or reducing the side effects of a serotonin uptake or re-uptake inhibitor (SRI) by administering an effective amount of a 5-HT_{1A} receptor antagonist to a mammal suffering from or susceptible to such side-effects.

Preferably the mammal is a human.

The 5-HT_{1A} receptor antagonist may be administered simultaneously, separately or sequentially relative to the SRI.

The method is particularly well suited to preventing or reducing sexual disfunction as a side effect of SRI treatment.

There is also provided the use of a 5-HT_{1A} receptor antagonist to prevent or reduce the side effects of an SRI.

There is also provided the use of a 5-HT_{1A} receptor antagonist in the manufacture of a medicament to prevent or reduce the side effects of an SRI.

It has also surprisingly been found that the onset of the therapeutic effects of SRIs can be hastened by simultaneous, separate or sequential administration of a 5-HT_{1A} receptor antagonist.

Accordingly, in a further aspect, the invention provides a method of treating neurological disorder such as depression or anxiety by simultaneous, separate or sequential administration of an effective amount of a 5-HT_{1A} receptor antagonist and an effective amount of an SRI to a mammal in need of such treatment

There is also provided the use of a 5-HT_{1A} receptor antagonist to accelerate, potentiate or otherwise enhance the therapeutic effect, especially the antidepressant or anxiolytic effect, of an SRI.

There is also provided the use of a 5-HT_{1A} receptor antagonist in the manufacture of a medicament to accelerate, potentiate or otherwise enhance the therapeutic effect, especially the antidepressant or anxiolytic effect, of an SRI.

Preferably, the 5-HT_{1A} receptor antagonist and the SRI are provided in synergistic amounts.

The term '5-HT_{1A} receptor antagonist' as used herein denotes a species which acts as an antagonist at the 5-HT (also known as 5-hydroxy tryptamine and/or serotonin) receptor designated subtype 1A. Preferably, the species used are selective 5-HT_{1A} antagonists.

By the term "selective 5-HT_{1A} antagonists" are meant compounds which:

(1) are highly potent ligands at the 5-HT_{1A} site having an IC_{50} value of 50nM or less (as determined by procedure A below).

(2) are at least 25 fold selective in terms of their IC_{50} values for the 5-HT_{1A} site compared with their IC_{50} values for other major monoamine receptor sites in the CNS (as determined by procedure B below).

(3) act as antagonists but not agonists in pharmacological models of 5-HT_{1A} receptor function (as determined by procedure C(a) or C(b) below).

Procedure (A)

The compounds are tested for the 5-HT_{1A} binding properties by measuring their ability to displace [^{3}H]-8-OH-DPAT from the 5-HT_{1A} receptor in rat hippocampal membranes according to the procedure of B.S. Alexander and M.D. Wood, J. Pharm. Pharmacol., 1988 40, 888-891. A compound is regarded as highly potent in this procedure if it has an IC_{50} of 50nM or less.

Procedure (B)

The affinity of the compounds for D_2 receptor sites is determined by the procedure of P. Seeman et al., J. Neurochem., 1984, 43, 221-235.

The affinity of the compound for α_1 sites is determined by the procedure of A.L. Morrow et al., Mol. Pharmacol., 1986, 29, 321.

The affinity of the compound for 5-HT_{2A} sites is determined by the procedure of R.A. Lyon et al., Mol. Pharmacol., 1987, 31, 194-199. (The 5-HT_{2A} site was previously known as the 5-HT_2 site).

A compound is regarded as being 25 fold selective if the IC_{50} value for each of the D_2, α_1 and 5-HT_{2A} sites as determined above is at least 25 times the IC_{50} value for the 5-HT_{1A} site as determined in Procedure (A). Preferably the compound should be 50 fold selective.

In addition to showing selectivity over the D_2, α_1 and 5-HT_{2A} sites it is also preferable that the compound is 25 fold selective (preferably 50 fold selective) over one or more of the 5-HT_{1B}, 5-HT_{2C}, 5-HT_{1D}, 5-HT_3, α_2, β and D_1 sites. The affinity for these sites is determined by the following procedures.

5-HT_{1B}: B.J. Alexander et al., Br. J. Pharmac., 1986, 87, P 22.

5-HT_{2C}: B.J. Alexander et al., Br. J. Pharmac., 1986, 87, P 22. (The 5-HT_{2C} site was previously known as the 5-HT_{1C} site).

5-HT_{1D}: C. Waeber et al., Naunyn-Schmiedebergs Arch. Pharmacol., 1988, 337, 595-601.

5-HT_3: N.M. Barnes et al., J. Pharm. Pharmacol., 1988, 40, 548-551.

α_2: D.J. Loftus et al., Life Sciences, 1984, 34, 61-69.

β: L.T. Williams and R. J. Lefkowitz (1987) Receptor binding studies in adrenergic pharmacology, Raven Press, New York.

D_1: V Billard et al., Life Sciences, 1984, 35, 1885-1893.

Procedure (C)

This procedure determines whether a compound that has 5-HT_{1A} binding activity (as determined by procedure (A) possesses agonist and/or antagonist activity. Brain 5-HT_{1A} receptors exist as two populations in the brain i.e. postsynaptic 5-HT_{1A} receptors and presynaptic somatodendritic 5-HT_{1A} receptors. The presynaptic receptors are particularly sensitive to the agonist properties of 5-HT_{1A} receptor ligands and are activated by compounds designated 'partial agonists', which function as antagonists at the postsynaptic receptor. "Partial agonists" dose-dependently activate presynaptic receptors but "antagonists" do not display significant agonist activity in models of either postsynaptic or presynaptic 5-HT_{1A} receptor function but act as antagonists in both types of model. The activation of presynaptic 5-HT_{1A} receptors results in the inhibition of serotonin neurones which can be quantified in two ways:-

(a) Electrophysiologically monitoring the activity of the neurones to measure their firing rate by the method of H.J. Haigler and G.K. Aghajanian, J. Pharmacol. Exp. Therap., 1974, 188, 688. An intravenous ID_{50} dose is determined. The agonist, 8-OH-DPAT, has an ID_{50} value of 1.9 µg/kg iv. Antagonists are those compounds which meet criteria (1) and (2) above, which do not induce a 50% reduction in neuronal firing rate below a dose of 500 µg/kg iv and which significantly ($p < 0.05$) increase the ID_{50} of the agonist 8-OH-DPAT.

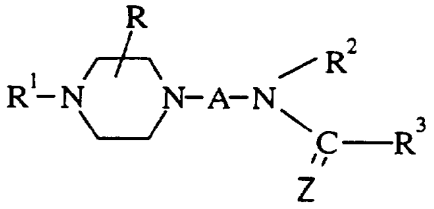
(b) Studying the effect on 5-HT release in the hippocampus using in vivo microdialysis according to the method of C. Routledge, J. Gurling, I. K. Wright and C.T. Dourish, Eur. J. Pharmacol. 239, 195-202, 107, 5P. Agonists and partial agonists

significantly reduce 5-HT release following subcutaneous administration, whereas antagonists do not significantly decrease 5-HT release but antagonise the decreased release induced by 8-OH-DPAT.

The term 'serotonin re-uptake inhibitor' as used herein denotes a species which inhibits the uptake or re-uptake of serotonin (also known as 5-HT and 5-hydroxy tryptamine) into nerve cells. Preferably, the inhibition is such as to provide an ED_{50} value (measured as described in EP-A-0228795) of less than 50 mg/kg, preferably less than 5 mg/kg.

Suitably the SRI is a selective serotonin re-uptake inhibitor such as sertraline, paroxetine, fluvoxamine, fluoxetine, femoxetine, citalopram, clomipramine, cianopramine, litoxetine, ericlamine or seproxetine or the compounds designated WY 27587 and WY 27866 (N-[[[1-[(6-Fluoro-2-naphtalenyl)methyl]-4-piperidinyl]amino)carbonyl]-3-pyridinecarboxamide, dihydrochloride, hemihydrate (EPO228795 John Wyeth & Brother Limited) and N-[[[1-(6-fluoro-2-naphhthalenyl methyl)-4-piperidinyl]amino]carbonyl]-6-quinolinecarboxamide, acid maleate (EP 234098 (John Wyeth & Brother Limited) respectively).

Compounds which are particularly suitable for use as $5\text{-}HT_{1A}$ antagonists include those of the general formula



(I)

and the pharmaceutically acceptable acid addition salts thereof.

In formula (I)

A is an alkylene chain of 2 to 4 carbon atoms optionally substituted by one or more lower alkyl groups,

Z is oxygen or sulphur,

R is hydrogen or lower alkyl,

R^1 is a mono or bicyclic aryl or heteroaryl radical,

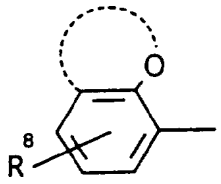
R^2 is a mono or bicyclic heteroaryl radical

and R^3 is hydrogen, lower alkyl, cycloalkyl, cycloalkenyl, cycloalkyl(lower)alkyl, aryl, aryl(lower)alkyl, heteroaryl, heteroaryl- (lower)alkyl, a group of formula $-NR^4R^5$ [where R^4 is hydrogen, lower alkyl, aryl or aryl-(lower)alkyl and R^5 is hydrogen, lower alkyl, -CO(lower)alkyl, aryl, COaryl, aryl(lower)alkyl, cycloalkyl or cycloalkyl-(lower)alkyl or R^4 and R^5 together with the nitrogen atom to which they are both attached represent a saturated heterocyclic ring which may contain a further hetero atom] or a group of formula OR^6 [where R^6 is lower alkyl, cycloalkyl, cycloalkyl(lower)alkyl, aryl, aryl(lower)alkyl, heteroaryl or heteroaryl(lower)alkyl].

The term "lower" as used herein means that the radical referred to contains 1 to 6 carbon atoms. Preferably such radicals contain 1 to 4 carbon atoms. Examples of "lower alkyl" radicals are methyl, ethyl, propyl, isopropyl, butyl, tert.-butyl, pentyl and isopentyl.

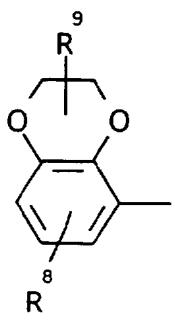
Examples of cycloalkyl groups are cyclopentyl, cyclohexyl and cycloheptyl. A preferred example is cyclohexyl. Cycloalkyl groups include bicyclic, tricyclic and tetracyclic groups, eg adamantyl. Preferably the cycloalkyl group contains 3 to 12 carbon atoms.

When used herein "aryl" means an aromatic radical having 6 to 10 carbon atoms (eg phenyl or naphthyl) which optionally may be substituted by one or more substituents. Preferred substituents are lower alkyl, lower alkoxy (eg methoxy, ethoxy, propoxy, butoxy), halogen, halo(lower)alkyl (eg trifluoromethyl), nitro, nitrile, amido, (lower)alkoxycarbonyl, amino, (lower)alkylamino or di(lower)alkylamino substituents. Two substituents on the aromatic ring may be connected together to form another ring system. For example R^1 may be an optionally substituted tetrahydronaphthyl radical or a bicyclic oxygen-containing radical of the formula

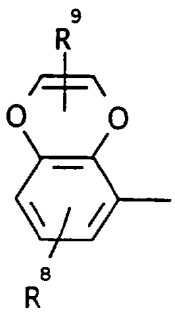


wherein the heterocyclic ring containing the oxygen atom contains a total of 5 to 7 ring members, said heterocyclic ring being saturated or unsaturated, being optionally substituted and optionally containing one or more hetero ring members (eg -O-, NR^7- where R^7 is hydrogen or lower alkyl, -S- or -SO_2-) in addition to the oxygen atom illustrated and wherein R^8 represents hydrogen or one or more same or different substituents selected from lower alkyl, halogen, oxo, hydroxy, (lower)alkoxy, hydroxy(lower)alkyl, (lower)alkoxy(lower alkyl), lower alkanoyloxy(lower alkyl), (lower)- alkylcarbonyl, (lower)alkylcarbonyl(lower)alkyl, amino, (lower)alkylamino or di(lower)alkylamino.

Preferred examples of a bicyclic oxygen-containing radical are those of the formulae



(a)



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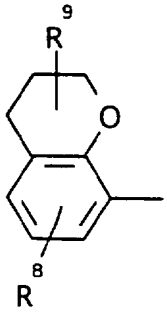
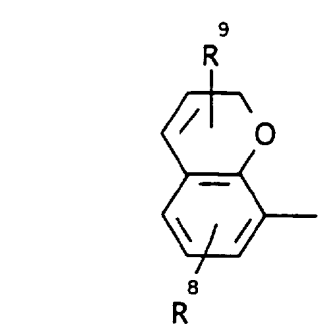
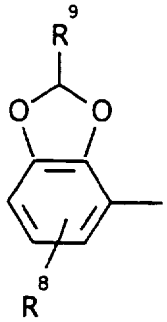


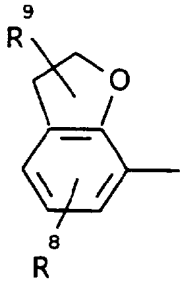
(c)



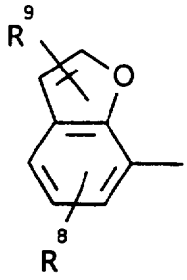
(d)



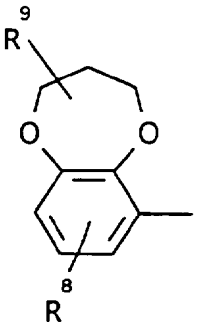
(e)

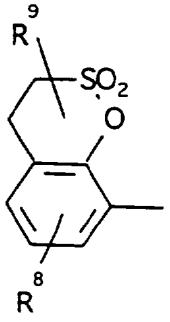


(f)

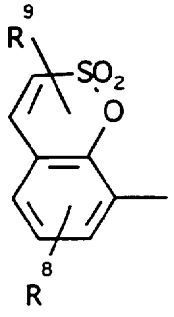


(g)



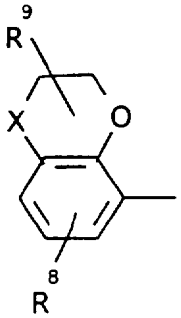


(i)



(j)

or



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where R^8 is as defined above, R^9 has the definition of R^8 given above and X is -CO-, -S-, or -NR^7- where R^7 is hydrogen or lower alkyl.

When R^1 is an aryl radical it is preferably a phenyl radical containing a substituent in the ortho position. A preferred example of R^1 is o-(lower)alkoxyphenyl eg o-

methoxyphenyl. R^1 can also be, for example a 1-naphthyl radical optionally substituted in the 2 or 7 positions by, for example, (lower)alkoxy.

Preferred examples of aryl(lower)alkyl are benzyl and phenethyl in which the phenyl rings may be substituted by substituents as given above.

The term "heteroaryl" refers to an aromatic radical containing one or more hetero atoms (eg oxygen, nitrogen, sulphur) and which may be optionally substituted by one or more substituents. Examples of suitable substituents are given above in connection with "aryl" radicals. The heteroaryl radical may, for example, contain up to 10 ring atoms. Preferably the heteroaryl radical is a monocyclic radical containing 5 to 7 ring atoms. Preferably the hetero ring contains a nitrogen hetero atom with or without one or more further hetero atoms. When R^1 is a heteroaryl radical it is preferably an optionally substituted pyrimidyl (particularly 2-pyrimidyl), isoquinolinyl (particularly 1-isoquinolinyl) or 1,2-benzisothiazolyl radical. When R^2 is a bicyclic heteroaryl radical both rings of the radical may contain hetero ring atoms or only one ring may contain a hetero atom or atoms. In the latter instance the radical R^2 is connected to the rest of the molecule of formula (I) via the ring containing the hetero atom(s).

Examples of the heteroaryl radical R^2 include monocyclic radicals containing one hetero atom, eg optionally substituted pyridyl (particularly 2-pyridyl), monocyclic radicals containing two hetero atoms, eg thiazolyl (particularly 2-thiazolyl) and bicyclic radicals containing one or two hetero atoms eg quinolinyl or isoquinolinyl (particularly 2-quinolinyl).

When R^4 and R^5 together with the nitrogen atom to which they are both attached represent a saturated heterocyclic ring this may be, for example, azetidino, pyrrolidino, piperidino, hexahydroazepino, morpholino or piperazino which may be optionally substituted by, for example, lower alkyl, aryl or aryl(lower)alkyl.

Preferred compounds have the following substituents either independently or in combination:-

(a) A is $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$ or $-CH(CH_3).CH_2-$

(b) R is hydrogen

(c) R^1 is o-methoxyphenyl, o-isopropylphenyl, 4-fluoro-2-methoxyphenyl, 2,3-dihydro[1,4]benzo-dioxan-5-yl), pyrimid-2-yl, 1-naphthyl,3-(1,2-benzisothiazolyl), 1-(7-methoxynapthyl) or 1-(5,6,7,8)-tetrahydronaphthyl

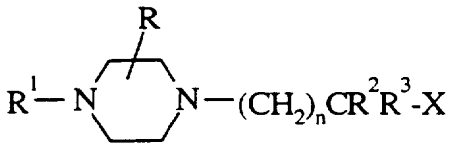
(d) R^2 is pyrid-2-yl, quinolin-2-yl or thiazol-2-yl

(e) R^3 is lower alkyl (eg methyl or t-butyl), cycloalkyl (eg cyclohexyl), cycloalkenyl (eg cyclohexenyl), phenyl, piperidino, adamantyl, or -NHcycloalkyl (eg -NHcyclohexyl)

(f) Z is oxygen

Compounds of formula I may be prepared as described in EP-A 512755 (Wyeth).

Further compounds suitable for use as 5-HT_{1A} antagonists are those of the general formula II



(II)

and the pharmaceutically acceptable acid addition salts thereof.

In formula (II)

n is one of the integers 1 or 2,

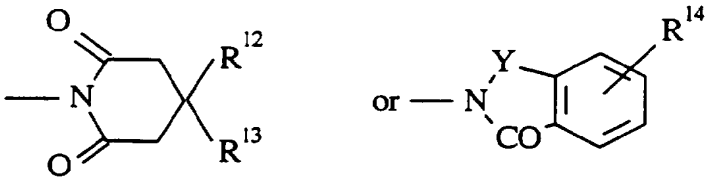
R is hydrogen or lower alkyl,

R^1 is an aryl or monocyclic nitrogen containing heteroaryl radical,

R^2 is hydrogen or lower alkyl,

R^3 is an aryl radical, an alkyl radical containing 4 to 8 carbon atoms or an aryl (lower) alkyl radical,

X is $-OCOR^{10}$, $-CO_2R^6$, $-CONR^5R^9$, $-OCO_2R^6$, $-NR^4COR^6$, $OCONHR^{11}$, $-NHCO_2R^6$, $-NR^4CONHR^6$, $-CONHNHR^6$, $-CONHOR^6$,



R^4 and R^5 are each hydrogen or lower alkyl

R^6 is $-CHR^7R^8$, cycloalkyl of 3 to 12 carbon atoms or aryl(lower)alkyl (where R^7 and R^8 are each hydrogen or lower alkyl),

R^9 is hydrogen, an alkyl group of 1 to 8 carbon atoms, cycloalkyl of 3 to 12 carbon atoms, cycloalkyl(lower)alkyl, aryl(lower)alkyl or 8-azaspiro[4.5]deca-7,9-dione-8-yl-(lower)alkyl

or R^5 and R^9 together with the nitrogen atom to which they are attached represent an azetidino, pyrrolidino, piperidino, hexahydroazepino, morpholino or piperazino ring which may be optionally substituted by lower alkyl, aryl or aryl(lower)alkyl,

R^{10} is cycloalkyl of 3 to 12 carbon atoms, or 2,3-dihydro[1,4]benzodioxinyl optionally substituted by lower alkyl, lower alkoxy or halogen,

R^{11} is cycloalkyl of 3 to 12 carbon atoms, aryl or aryl(lower)alkyl,

R^{12} and R^{13} are each lower alkyl or together with the carbon atom to which they are both attached represent C_{4-6} cycloalkyl,

R^{14} represents hydrogen, halogen, lower alkyl or lower alkoxy
and
Y is CO or SO_2 .

The term "lower" as used in formula II means that the radical referred to contains 1 to 6 carbon are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert.-butyl, pentyl and isopentyl. When R^3 is an alkyl group of 4 to 8 carbon atoms it may be a straight or branched chain group; a preferred example is tert.-butyl. Preferably R^3 is an aryl radical.

In formula II "aryl" means an aromatic radical having 6 to 12 carbon atoms (eg phenyl, naphthyl) which optionally may be substituted by one or more substituents commonly used in medicinal chemistry, eg substituents such as lower alkoxy, halogen, trifluoromethyl, nitro, carbalkoxy, carboxamido, cyano, amino, (lower)alkylamino and di(lower)alkylamino.

Examples of aryl(lower)alkyl and aryl(lower)alkoxy include, for example, benzyl and benzyloxy in which the phenyl group may be substituted as defined above.

In formula II "nitrogen containing heteroaryl radical" means an aromatic ring containing one or more nitrogen atoms as heteroatoms (eg pyridinyl, pyrimidinyl or pyrazinyl) which may optionally be substituted by one or more lower alkyl, lower alkoxy, halogen, trifluoromethyl, amino, (lower)alkylamino or di(lower)alkylamino substituents. Preferably the heteroaryl radical is monocyclic.

Preferred compounds of formula II are:-

those in which n is 1;

those in which R^1 is aryl particularly an optionally substituted phenyl such as o-methoxphenyl;

those in which R is hydrogen;

those in which R^2 is hydrogen;

those in which R^3 is aryl particularly optionally substituted phenyl;

those in which X is an ester grouping of formula $-CO_2R^6$ or an amide grouping of formula $-CONR^5R^9$ particularly where $-NR^5R^9$ represents a cyclic grouping eg piperidino or hexahydroazepino.

Compounds of formula II may be prepared as described in EP-A-395312 (Wyeth). Both the 5-HT_{1A} receptor antagonist and the serotonin re-uptake inhibitor may be provided in the form of pharmaceutically acceptable salts, if desired.

Further piperazine derivatives and their methods of preparation are disclosed, for example, in

GB 2230780A;
GB 2230781A;
GB 2248836A;
and GB 2255337A

The compounds disclosed in GB 2230780A are described as antidepressant and/or anxiolytic agents. The compounds disclosed in GB 2230781A, GB 2248836A and GB 2255337A are disclosed as 5-HT_{1A} antagonists useful for the treatment of CNS disorders such as anxiety, as antidepressants, hypotensives and as agents for regulating the sleep/wake cycle, feeding behaviours and/or sexual function.

Particularly preferred compounds of the present invention are:

N-tert-butyl-3-[4-(2-methoxyphenyl)piperazin-1-yl]-2-phenylpropanamide and its (S)-enantiomer

2,3,4,5,6,7-hexahydro-1-[4-[1-[4-(2-methoxyphenyl)-piperazinyl]]-2-phenyl]butanoyl-1H-azepine

(-)-(R)-2,3,4,5,6,7-hexahydro-1-[4-[4-(2-methoxyphenyl)piperazin-1-yl]-2-phenyl]butanoyl-1H- azepine

N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-(2-pyridinyl)cyclohexanecarboxamide

and their pharmaceutically acceptable acid addition salts.

The 5-HT_{1A} receptor antagonist can be administered by any suitable means and is typically administered orally, enterally, parenterally, sublingually or transdermally.

Preferably, the 5-HT_{1A} receptor antagonist is administered as a pharmaceutical composition in association with a pharmaceutically acceptable carrier. Any suitable carrier known in the art can be used to prepare the pharmaceutical composition. In such a composition, the carrier is generally a solid or liquid or a mixture of a solid or liquid.

Solid form compositions include powders, granules, tablets, capsules (eg hard and soft gelatine capsules), suppositories and pessaries. A solid carrier can be, for example, one or more substances which may also act as flavouring agents, lubricants, solubilisers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents. It can also be an encapsulating material. In powders the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99%, eg from 0.03 to 99%, preferably 1 to 80% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidine, low melting waxes and ion exchange resins.

The term "composition" is intended to include the formulation of an active ingredient with encapsulating material as carrier to give a capsule in which the active ingredient

(with or without other carriers) is surrounded by the carrier, which is thus in association with it. Similarly cachets are included.

Liquid form compositions include, for example, solutions, suspensions, emulsions, syrups, elixirs and pressurised compositions. The active ingredient, for example, can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fats. The liquid carrier can contain other suitable pharmaceutical additives such as solubilisers, emulsifiers, buffers, preservatives, sweeteners, flavouring agents, suspending agents, thickening agents, colours, viscosity regulators, stabilisers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (particularly containing additives as above, eg cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (eg glycerol and glycols) and their derivatives, and oils (eg fractionated coconut oil and arachis oil). For parenteral administration the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are used in sterile liquid form compositions for parenteral administration.

Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. When the compound is orally active it can be administered orally either in liquid or solid composition form.

Preferably the pharmaceutical composition is in unit dosage form, eg as tablets or capsules. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged compositions, for example packeted powders, vials, ampoules, prefilled syringes or sachets containing liquid. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form. The quantity of the active ingredient in unit dose of composition may be varied or adjusted from 0.5 mg or less to 750 mg or more, according to the particular need and the activity of the active ingredient.

The present invention further provides the use of a 5-HT_{1A} receptor antagonist to prevent or reduce the side effects of a serotonin uptake or re-uptake inhibitor.

There is further provided the use of a 5-HT_{1A} receptor antagonist in the manufacture of a medicament to prevent or reduce the side effects of a serotonin uptake or re-uptake inhibitor.

Suitably, in such cases, the 5-HT_{1A} receptor antagonist, serotonin re-uptake inhibitor and dosage forms are as described above. Suitably, the 5-HT_{1A} receptor antagonist is used to prevent or reduce sexual disfuction.

According to a further aspect of the invention there is provided a product comprising i) a 5-HT_{1A} receptor antagonist and ii) a serotonin re-uptake inhibitor as a combined preparation for simultaneous, separate or sequential use in treating or preventing neurological disorders.

There is further provided a pharmaceutical composition comprising i) a 5-HT_{1A} receptor antagonist and ii) a serotonin re-uptake inhibitor in combination with a pharmaceutically acceptable carrier.

The invention is illustrated by the following Examples:

Example 1

Preparation of Tablets

	Amount per tablet mg		
(-)-(R)-2,3,4,5,6,7-Hexahydro-1-[4-[4-(2-methoxyphenyl)piperazin-1-yl]-2-phenyl]butanoyl-1H-azepine	1	5	10
Microcrystalline cellulose	49.25	47.25	44.75
Modified food corn starch	49.25	47.25	44.75
Magnesium stearate	0.5	0.5	0.5

Tablets are prepared from bulk amounts of ingredients in the proportions given above.

All of the active compound, cellulose and a portion of the corn starch are mixed and granulated to 10% corn starch paste. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium stearate. The resulting granulation is then compressed into tablets containing 1, 5 and 10 mg of the active ingredient per tablet.

Example 2

Preparation of powder filled capsules

	Amount mg	
N-tert.butyl-3-[4-(2-methoxyphenyl)piperazin-1-yl]-2-phenylpropanamide	10	15
Avicel	45	
Lactose	153	
Starch (1500 NF)	-	117
Sodium starch glycollate	-	6
Magnesium stearate	2	2

The formulations are prepared by admixing the ingredients in the proportions given above and filling two-part hard gelatin capsules with the required amount of the resulting mixture to give capsules containing 10 or 15 mg of the active compound.

Example 3

Reverse-daylight entrained male Wistar rats were isolated for 3 days prior to and throughout the experiment and subjected to daily social encounters with an unfamiliar intruder rat. After the first encounter separate osmotic minipumps (Alzet 2002) containing vehicle (saline), fluoxetine or N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-(2-pyridinyl)cyclohexanecarboxamide, trihydrochloride, hydrate, were implanted subcutaneously. The behavioural profiles of the resident rats during each social encounter were analysed ethologically as described in Mitchell and Redfern (J. Psychopharmacol. (1992) **6,** 241-257). Data were analysed using ANOVA after root transformation, followed by a *post-hoc* t-test. Fluoxetine (Flu) was administered at 0.3 mg/kg/day and N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-(2-pyridinyl)cyclohexanecarboxamide, trihydrochloride, hydrate (Cpd A) was administered at 0.1 mg/kg/day (both via sub-cutaneously implanted mini-pumps). Results for aggressive and sexual (attempt mount and 'lick penis') behaviours are set out in Tables 1 and 2 respectively below.

Table 1 (aggressive behaviour)

Treatment	Pre-dose	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	2-way ANOVA
H_2O/ Saline	4.6 ±0.6	6.6 ±0.6	6.3 ±0.5	6.3 ±0.7	6.8 ±0.9	6.3 ±0.6	5.7 ±0.7	7.5 ±0.6	
Flu/ Saline	5.1 ±0.3	5.4 ±0.6	5.5 ±0.7	6.3 ±0.4	6.9 ± 0.6	10.9 ±0.5*	13.7 ±0.6*	14.6 ±1.1*	13.605 P < 0.0001
H_2O/ Cpd A	4.8 ±0.6	6.7 ±0.4	7.3 ±0.8	7.4 ± 0.4	7.1 ±0.6	6.8 ±0.6	7.0 ±0.4	6.5 ±0.6	0.830 NS
Flu/ Cpd A	5.1 ±0.6	10.0 ±1.9	10.7 ±1.5*§	12.2 ±1.1*§	12.8 ±1.4*§	13.0 ±1.2*	16.2 ±1.0*	16.3 ±1.6*	6.203 P < 0.0001

In table 1, aggressive behaviour of resident rats is given as mean % of total behaviours ± SEM (standard error mean).

* denotes $P < 0.05$ in the t-test compared to water/saline.

§ denotes $P < 0.05$ in the t-test compared to fluoxetine/saline.

3-way ANOVA, $F(7,196) = 2.279$, $P < 0.05$ (comparison of all treatments with repeated measures over the course of experiment).

2-way ANOVA, F (7,98) compared to water/saline.

It will be seen from table 1 that resident rats treated with drug vehicles or N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-(2-pyridinyl)cyclohexanecarboxamide, trihydrochloride, hydrate (Cpd A) showed no significant change in their aggressive

behaviour during the period of treatment. Fluoxetine/saline treatment increased aggressive behaviour from day 5, whilst fluoxetine/Cpd A combination treatment increased aggressive behaviour from day 2. These results demonstrate that the selective 5-HT 1A receptor antagonist N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-(2-pyridinyl)cyclohexanecarboxamide, trihydrochloride, hydrate (Cpd A) accellerates the behavioural effect of the SRI fluoxetine in an animal model predictive of antidepressant activity.

Table 2 (sexual behaviour)

Treatment	Pre-dose	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	2-way AN-OVA
H_2O/ Saline	3.5 ±0.9	1.9 ±0.6	1.2 ±0.3	2.9 ±0.9	1.2 ±0.4	1.7 ±0.8	0.8 ±0.5	0.9 ±0.4	1.599 P>0.05
Flu/ Saline	4.9 ±0.9	5.9 ±1.2	5.3 ±1.2	5.6 ±1.2	4.3 ±1.3	4.0 ±1.3	3.0 ±0.6	1.6 ±0.5	
H_2O/ Cpd A	2.3 ±0.8	1.1 ±0.4	2.0 ±1.1	0.4 ±0.1	0.3 ±0.1	0.4 ±0.1	0.5 ±0.2	0.6 ±0.4	
Flu/ Cpd A	3.1 ±1.0	0.9 ±0.3**	0.6 ±0.4**	0.5 ±0.2**	0.8 ±0.4*	1.1 ±0.8	0.7 ±0.5*	0.3 ±0.2	3.043 P<0.05

In table 2, sexual behaviour of resident rats is given as mean % of total behaviours ± SEM (standard error mean).

* denotes $P < 0.05$ in the t-test compared to fluoxetine/saline.

** denotes $P < 0.01$ in the t-test compared to fluoxetine/saline.

3-way ANOVA, $F(7,196) + 2.331$, $P < 0.05$ (comparison of all treatments with repeated measures over the course of experiment).

2-way ANOVA compared to fluoxetine/saline.

It will be seen from table 2 (2-way ANOVA) that treatment with fluoxetine/Cpd A was significantly different from treatment with fluoxetine/saline. The t-test shows that rats treated with fluoxetine/Cpd A showed significantly lower sexual behaviours on days 1 to 4 and 6 than rats treated with fluoxetine/saline.

CLAIMS

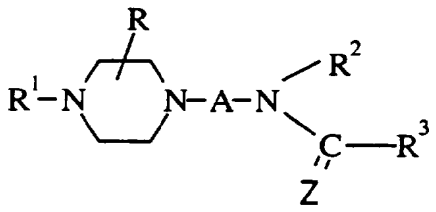
1. The use of a 5-HT_{1A} or 5-HT_2 receptor antagonist in the manufacture of a medicament to prevent or reduce the side effects of a serotonin re-uptake inhibitor

2. The use of a 5-HT_{1A} or 5-HT_2 receptor antagonist in the manufacture of a medicament to accelerate, potentiate or otherwise enhance the therapeutic effect, especially the antidepressant or anxiolytic effect, of a serotonin re-uptake inhibitor.

3. A use as claimed in claim 1 or claim 2 wherein the serotonin reuptake inhibitor is a selective serotonin re-uptake inhibitor selected from sertraline, paroxetine, fluvoxamine, fluoxetine, femoxetine, citalopram, clomipramine, cianopramine, litoxetine, ericlamine and seproxetine

4. A use as claimed in any one of the preceding claims wherein a 5-HT_{1A} receptor antagonist is used.

5. A use as claimed in claim 4 wherein the 5-HT_{1A} receptor antagonist is a compound of the general formula



(I)

and the pharmaceutically acceptable acid addition salts thereof.

In formula (I)

A is an alkylene chain of 2 to 4 carbon atoms optionally substituted by one or more lower alkyl groups,

Z is oxygen or sulphur,

R is hydrogen or lower alkyl,

R^1 is a mono or bicyclic aryl or heteroaryl radical,

R^2 is a mono or bicyclic heteroaryl radical

and R^3 is hydrogen, lower alkyl, cycloalkyl, cycloalkenyl, cycloalkyl(lower)alkyl, aryl, aryl(lower)alkyl, heteroaryl, heteroaryl- (lower)alkyl, a group of formula $-NR^4R^5$ [where R^4 is hydrogen, lower alkyl, aryl or aryl-(lower)alkyl and R^5 is hydrogen, lower alkyl, -CO(lower)alkyl, aryl, COaryl, aryl(lower)alkyl, cycloalkyl or cycloalkyl-(lower)alkyl or R^4 and R^5 together with the nitrogen atom to which they are both attached represent a saturated heterocyclic ring which may contain a further hetero atom] or a group of formula OR^6 [where R^6 is lower alkyl, cycloalkyl, cycloalkyl(lower)alkyl, aryl, aryl(lower)alkyl, heteroaryl or heteroaryl(lower)alkyl].

6. A use as claimed in claim 5 wherein the 5-HT_{1A} receptor antagonist has the following substituents either independently or in combination:-

(a) A is $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$ or $-CH(CH_3).CH_2-$

(b) R is hydrogen

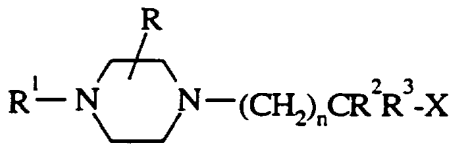
(c) R^1 is o-methoxyphenyl, o-isopropylphenyl, 4-fluoro-2-methoxyphenyl, 2,3-dihydro[1,4]benzo-dioxan-5-yl), pyrimid-2-yl, 1-naphthyl,3-(1,2-benzisothiazolyl), 1-(7-methoxynapthyl) or 1-(5,6,7,8)-tetrahydronaphthyl

(d) R^2 is pyrid-2-yl, quinolin-2-yl or thiazol-2-yl

(e) R^3 is lower alkyl (eg methyl or t-butyl), cycloalkyl (eg cyclohexyl), cycloalkenyl (eg cyclohexenyl), phenyl, piperidino, adamantyl, or -NHcycloalkyl (eg -NHcyclohexyl)

(f) Z is oxygen

7. A use as claimed in any one of claims 1 to 4 wherein the 5-HT_{1A} antagonist is a compound of the general formula II



(II)

and the pharmaceutically acceptable acid addition salts thereof.

wherein:

n is one of the integers 1 or 2,

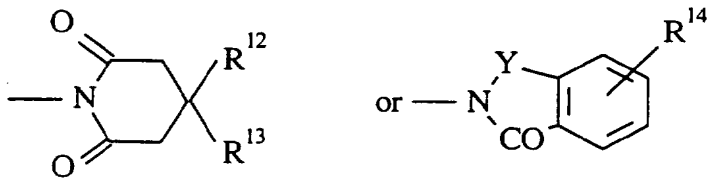
R is hydrogen or lower alkyl,

R^1 is an aryl or monocyclic nitrogen containing heteroaryl radical,

R^2 is hydrogen or lower alkyl,

R^3 is an aryl radical, an alkyl radical containing 4 to 8 carbon atoms or an aryl (lower) alkyl radical,

X is $-OCOR^{10}$, $-CO_2R^6$, $-CONR^5R^9$, $-OCO_2R^6$, $-NR^4COR^6$, $OCONHR^{11}$, $-NHCO_2R^6$, $-NR^4CONHR^6$, $-CONHNHR^6$, $-CONHOR^6$,



R^4 and R^5 are each hydrogen or lower alkyl

R^6 is $-CHR^7R^8$, cycloalkyl of 3 to 12 carbon atoms or aryl(lower)alkyl (where R^7 and R^8 are each hydrogen or lower alkyl),

R^9 is hydrogen, an alkyl group of 1 to 8 carbon atoms, cycloalkyl of 3 to 12 carbon atoms, cycloalkyl(lower)alkyl, aryl(lower)alkyl or 8-azaspiro[4.5]deca-7,9-dione-8-yl-(lower)alkyl

or R^5 and R^9 together with the nitrogen atom to which they are attached represent an azetidino, pyrrolidino, piperidino, hexahydroazepino, morpholino or piperazino ring which may be optionally substituted by lower alkyl, aryl or aryl(lower)alkyl,

R^{10} is cycloalkyl of 3 to 12 carbon atoms, or 2,3-dihydro[1,4]benzodioxinyl optionally substituted by lower alkyl, lower alkoxy or halogen,

R^{11} is cycloalkyl of 3 to 12 carbon atoms, aryl or aryl(lower)alkyl,

R^{12} and R^{13} are each lower alkyl or together with the carbon atom to which they are both attached represent C_{4-6} cycloalkyl,

R^{14} represents hydrogen, halogen, lower alkyl or lower alkoxy
and
Y is CO or SO_2 .

8. A use as claimed in claim 7 wherein the 5-HT_{1A} receptor antagonist has the following substituents either independently or in combination:-

n is 1;

R^1 is aryl particularly an optionally substituted phenyl such as o-methoxphenyl;

R is hydrogen;

R^2 is hydrogen;

R^3 is aryl particularly optionally substituted phenyl;

X is an ester grouping of formula $-CO_2R^6$ or an amide grouping of formula $-CONR^5R^9$ particularly where $-NR^5R^9$ represents a cyclic grouping eg piperidino or hexahydroazepino.

9. A use as claimed in any one of claims 1 to 3 wherein the 5-HT1A antagonist is:

N-tert-butyl-3-[4-(2-methoxyphenyl)piperazin-1-yl]-2-phenylpropanamide and its (S)-enantiomer

2,3,4,5,6,7-hexahydro-1-[4-[1-[4-(2-methoxyphenyl)-piperazinyl]]-2-phenyl]butanoyl-1H-azepine

(-)-(R)-2,3,4,5,6,7-hexahydro-1-[4-[4-(2-methoxyphenyl)piperazin-1-yl]-2-phenyl]butanoyl-1H- azepine; or

N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-

N-(2-pyridinyl)cyclohexanecarboxamide

and their pharmaceutically acceptable acid addition salts.

10. A product comprising i) a 5-HT_{1A} or 5-HT_2 receptor antagonist and ii) a serotonin re-uptake inhibitor as a combined preparation for simultaneous , separate or sequential use in treating or preventing neurological disorder, especially anxiety or depression.

11. A pharmaceutical composition comprising i) a 5-HT_{1A} or 5-HT_2 receptor antagonist and ii) a serotonin re-uptake inhibitor as a combined preparation for simultaneous , separate or sequential use in treating or preventing neurological disorder, especially anxiety or depression.

The Patent Office

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Application No:	GB 9614578.4	**Examiner:**	Mr S.J.Pilling
Claims searched:	1 to 11	**Date of search:**	15 October 1996

Patents Act 1977
Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.O): A5B (BHA, BJA, BJB)

Int Cl (Ed.6): A61K 31/495

Other: ONLINE: CAS ONLINE, WPI

Documents considered to be relevant:

Category	Identity of document and relevant passage		Relevant to claims
P,X	EP 0722941 A2	(LILLY) see page 97 lines 37 to 48, page 99 lines 2 to 4 and Claim 19.	2,10,11
P,X	WO 96/03400 A1	(PFIZER) see page 8 line 21 to page 9 line 6 and the final three claims.	2,10,11
A	US 4698342	(CROSBY) see the abstract.	-
X	TIPS, Vol. 14, July 1993, F Artigas, *"5 HT and antidepressants: new views from microdialysis studies"*, page 262, see particularly the final column.		1-11

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
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